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Transannular Nitrogen–Carbonyl Interaction in Cyclic Aminoketones and Optical Rotatory Dispersion[1,2]

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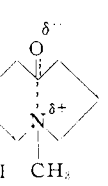
The optically active cyclic aminoketone, (+)-1-(α-methylphenethyl)-1-azacyclooctan-5-one (V), which exhibits transannular N–C_{CO} interaction as shown by its infrared spectrum, shows abnormal rotatory dispersion—specifically, a negative Cotton effect superimposed on a positive plain curve. Thus, the asymmetry of the α_N-carbon exerts its influence on carbonyl diametric, but conformationally in close proximity, to the nitrogen across the eight-membered ring. The rotatory dispersion for the open-chain analog, (+)-5-(N-ethyl-α-methylphenethylamino)-2-pentanone (IX), in which there is no N–C_{CO} interaction, exhibits no anomaly. The general shape of the positive plain curve for the latter is not altered by protonation, whereas the conjugate acid of the eight-membered ring aminoketone V, which is in the O-protonated form in solution (XI), has a markedly different dispersion curve from that of the base.

To the considerable body of physical and chemical evidence for the occurrence of transannular nitrogen–carbonyl interaction[6,7] in cyclic aminoketones and aminoacyloins of medium ring size (*e.g.*, I) has been added recently[1] that derived from dipole moment measurements, affirming the partial charge separation accompanying such interaction.



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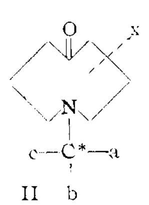
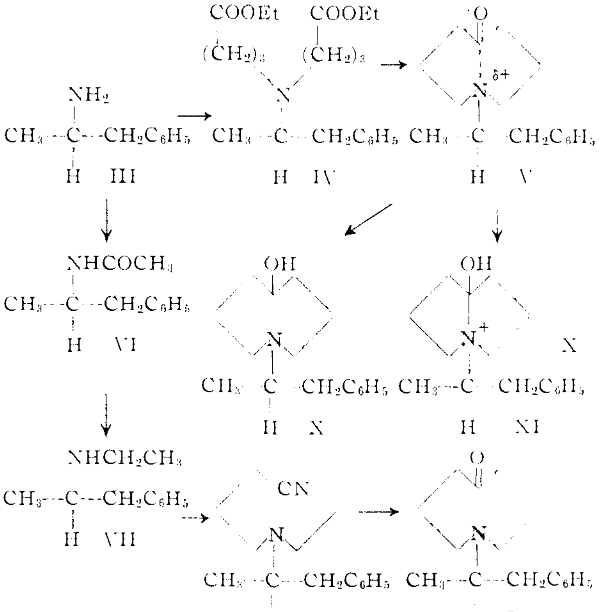


II

A possible additional demonstration of transannular interaction was sought in the optical rotatory dispersion method,[8,9] which has been developed systematically for the solution of structural and configurational problems. In order to trace the interplay of transannular N–C_{CO} interaction and abnormal rotatory dispersion, we desired an optically active model such as II in which the asymmetry of the α_N-carbon might exert its influence on the carbonyl diametric, but conformationally in close proximity, to the nitrogen. A second optically active model would then be required, such as might be visualized by a hypothetical hydrogenolytic scission of the eight-membered ring in II at x, thereby maintaining comparable structural features to those in II but releasing the carbonyl from enforced proximity to nitrogen.

The optically active amine which was selected as the synthetic precursor for the desired cyclic and open-chain aminoketones was (+)-α-methylphenethylamine (dextroamphetamine). This amine may be described further as D(+)-α-methylphenethylamine or as (+)-αR-methylphenethylamine,[10,11] since the absolute configuration (III) has been determined by Karrer[12,13] by direct conversion from D(+)-phenylalanine through D(+)-phenylalaninol, confirming the configuration arrived at earlier but indirectly by Leithe.[14] The configuration at the asymmetric carbon remains unchanged in the compounds IV-XI, here derived from III. The condensation of D(+)-α-methylphenethylamine with ethyl γ-iodobutyrate in the presence of potassium carbonate furnished diethyl (+)-γ,γ′-(α-methylphenethylimino)-bis-butyrate (IV) in 42% yield and (+)-1-(α-methylphenethyl)-2-pyrrolidone as a by-product. Dieckmann cyclization of the iminodiester IV with sodium hydride[15] in xylene under conditions of high dilution and high-speed stirring,[16]



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[1] Part X in the series on Cyclic Aminoacyloins and Aminoketones; for part IX, see N. J. Leonard, D. F. Morrow and M. T. Rogers, THIS JOURNAL, **79**, 5476 (1957).

[2] Part XX in the series on Optical Rotatory Dispersion Studies; for part XIX, see C. Djerassi, D. Marshall and T. Nakano, *ibid.*, **80**, 4853 (1958).

[3] Monsanto Chemical Co. Fellow, 1955–1956.

[4] National Science Foundation Fellow, 1956–1957.

[5] Supported by Grant No. CY-2919 from the National Cancer Institute, National Institutes of Health.

[6] N. J. Leonard, *Rec. Chem. Progr.*, **17**, 243 (1956).

[7] N. J. Leonard and M. Ōki, *J. Japan Chem.*, **10**, 1003 (1956).

[8] C. Djerassi, *Bull. soc. chim. France*, 741 (1957).

[9] C. Djerassi, Abstracts, Fifteenth Organic Chemistry Symposium of the American Chemical Society, Rochester, N. Y., June, 1957, p. 12.

[10] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956).

[11] R. S. Cahn and C. K. Ingold, *J. Chem. Soc.*, 612 (1951).

[12] P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

[13] P. Karrer, P. Portmann and M. Suter, *ibid.*, **31**, 1617 (1948).

[14] W. Leithe, *Ber.*, **65B**, 660 (1932).

[15] F. F. Blicke, J. Azuara, N. J. Doorenbos and E. B. Hotelling, THIS JOURNAL, **75**, 5418 (1953).

[16] N. J. Leonard, M. Ōki and S. Chiavarelli, *ibid.*, **77**, 6234 (1955).

followed by hydrolysis and decarboxylation, yielded (55%) (+)-1-(α-methylphenethyl)-1-azacyclooctan-5-one (V). Transannular N–C_{CO} interaction in V was indicated by infrared absorption. The carbonyl band in the spectrum (10% solution in chloroform) was centered at 1686 cm.$^{-1}$, suggesting an interaction qualitatively equivalent to that observed for 1-cyclohexyl-1-azacycloöctan-5-one (1687 cm.$^{-1}$).[16] Transannular reaction, with development of a full bond between nitrogen and carbon, was observed when the conjugate acid was formed; thus, the perchlorate of V exhibited, as the solid (Nujol mull), a strong infrared absorption band at 3320 cm.$^{-1}$ and no absorption in the 6μ region and could therefore be assigned the O-protonated structure XI (X = ClO_4).

The synthesis of the open-chain analog IX of V was accomplished by a straightforward sequence, starting with the acetylation of D(+)-α-methylphenethylamine.[17] The (−)-N-(α-methylphenethyl)-acetamide (VI) was reduced with lithium aluminum hydride in tetrahydrofuran to (+)-N-ethyl-α-methylphenethylamine (VII), which was treated with γ-bromobutyronitrile and potassium carbonate to yield (+)-γ-(N-ethyl-α′-methylphenethylamino)-butyronitrile (VIII). The final step to the ketone (+)-5-(N-ethyl-α-methylphenethylamino)-2-pentanone (IX) involved the reaction of the nitrile VIII with methylmagnesium iodide. The final product IX contained a normal ketonic carbonyl as indicated by the strong infrared maximum at 1720 cm.$^{-1}$ (2% solution in carbon tetrachloride), and the oily perchlorate was N-protonated.

The accompanying figure shows the rotatory dispersion curves for the compounds of major interest. The rotatory dispersion for the open-chain aminoketone (+)-5-(N-ethyl-α-methylphenethylamino)-2-pentanone (IX) follows a positive plain curve[18] for the wave length region observed.[19] The general shape of the curve is not altered by protonation, as the rotatory dispersion of IX in 2 *N* hydrochloric acid also follows a positive plain curve. By contrast, the rotatory dispersion of the eight-membered ring aminoketone (+)-1-(α-methylphenethyl)-1-azacycloöctan-5-one (V) shows a considerable negative Cotton effect superimposed on a positive plain curve. In order for the asymmetric carbon to produce anomalous rotatory dispersion in V but not in IX, significant N–C_{CO} electronic interaction must occur in V.[20] Effectively, the asymmetric carbon is then the second atom removed from the carbonyl carbon in V. Other work in one of our laboratories on the effect of methyl groups[21,22] on the rotatory dispersion of asymmetric ketones has included the finding that optically active 3-methylcycloheptanone shows abnormal rotatory dispersion while the corresponding 4-methylcycloheptanone does not.[23] Thus, asymmetry at the second atom removed from the carbonyl is effective, and at the third atom removed is not effective, in promoting abnormal dispersion in these examples.

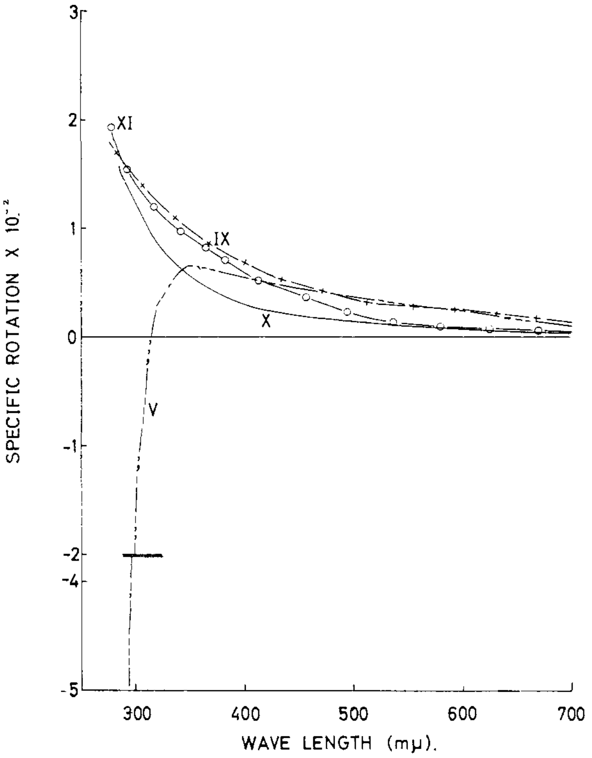

Fig. 1.—Optical rotatory dispersion curves of (+)-1-(α-methylphenethyl)-1-azacycloöctan-5-one (V) (methanol), (+)-5-(N-ethyl-α-methylphenethylamino)-2-pentanone (IX) (methanol), (+)-1-(α-methylphenethyl)-1-azacycloöctan-5-ol (X) (methanol) and of (+)-1-(α-methylphenethyl)-1-azacycloöctan-5-one in 2 *N* HCl (XI, X = Cl).

When the ultraviolet-absorbing group in V was removed, by lithium aluminum hydride reduction to (+)-1-(α-methylphenethyl)-1-azacycloöctan-5-ol (X), the effect on the rotatory dispersion was as expected: the aminoalcohol X shows a positive plain curve (Fig. 1) as does also the hydrochloride salt. The other method of "removal" of the ketone grouping was to form the hydrochloride salt of (+)-1-(α-methylphenethyl)-1-azacycloöctan-5-one (V). A solution of V in 2 *N* hydrochloric acid has a positive plain curve of wave length *vs.* specific rotation (Fig. 1). The normal curve may be explained either by N-protonation blocking transannular N–C_{CO} interaction or by O-protonation (XI, X = Cl) destroying the carbonyl function. The latter explanation is definitely preferred, since an independent infrared study has shown that the hydrochloride of V in deuterium oxide (*ca.* 40% solution), using a calcium fluoride cell, exhibits very little if any carbonyl absorption. It will be remembered that 1-ethyl-1-azacyclononan-5-ol-6-one (XIIb), as the perchlorate in D_2O, was also transparent in the infrared carbonyl region, indicating that the conjugate acid of this nine-

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[17] L. H. Welsh, *J. Assoc. Off. Agr. Chem.*, **36**, 714 (1953).

[18] For nomenclature, see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

[19] Methanol was used as the solvent throughout (unless otherwise stated).

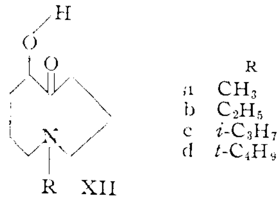
[20] For anomalous ultraviolet absorption of transannular-interacting aminoketones, see N. J. Leonard and M. Ōki, THIS JOURNAL, **77**, 6239 (1955).

[21] C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *ibid.*, **80**, 4001 (1958).

[22] E. J. Eisenbraun, J. Osiecki and C. Djerassi, *ibid.*, **80**, 1261 (1958).

[23] C. Djerassi and G. Krakower, unpublished results.

membered ring aminoacyloin is in the transannular quaternary form in solution.[24] By contrast, the perchlorates of both the 1-isopropyl and the 1-*t*-butyl analogs (XIIc, d) exhibited carbonyl maxima at 1706 ± 3 cm.$^{-1}$ in D_2O solution. In a more careful infrared study of these perchlorates in solution, comparing the relative intensities of C=O and C—H stretchings and assuming the 1-*t*-butyl-1-azacyclononan-5-ol-6-one (XIId) perchlorate to be 100% in the N-protonated form, it now appears that the 1-isopropyl-1-azacyclononan-5-ol-6-one (XIIc) perchlorate is about 20–25% in the N-protonated form. Thus, considerable O-protonated form must be recognized as existing in an aqueous solution of the conjugate acid of XIIc. Derivatives of 1-methyl-1-azacyclononan-5-ol-6-one (XIIa) which retain the carbonyl group partially or completely are the methiodide (not analyzed) and the benzobromide. The picrate of XIIa exhibits no infrared carbonyl absorption and is thus O-protonated as the solid, as is the perchlorate, solid[25] and solution.[24]



XII

Acknowledgment.—The authors are deeply indebted to Dr. Harold Boaz, Eli Lilly and Co., Indianapolis, Ind., for his interest and for the special infrared determinations in deuterium oxide solution. A generous gift of (+)-α-methylphenethylamine (dextroamphetamine) from Dr. Glenn E. Ullyot of Smith, Kline and French Laboratories, Philadelphia, Pa., made possible the synthesis of most of the compounds herein described, and we offer him our sincere thanks.

Experimental[26]

Optical Rotatory Dispersion Measurements.—The experimental procedure, limits of error and accepted methods for reporting rotatory dispersion data have been described previously.[18,27–29]

Diethyl (+)-γ,γ'-(α-Methylphenethylimino)-bis-butyrate (IV).—A mixture of 13.52 g. (0.10 mole) of (+)-α-methylphenethylamine (III), 48.42 g. (0.20 mole) of ethyl γ-iodobutyrate and 27.6 g. (0.20 mole) of potassium carbonate in 100 ml. of absolute ethanol[16] was stirred under reflux for 5 hours. The mixture was cooled and filtered, and the salts were washed with two 40-ml. portions of ethanol. The ethanol was removed at reduced pressure, and the residue was dissolved in 200 ml. of ether. The ethereal solution was washed with 50 ml. of water, dried, and the ether was removed on the steam-bath. The residue was distilled at reduced pressure through a Holzman column. A forerun was obtained, weight 8.55 g., b.p. 126–129° (0.3 mm.), n^{25}D 1.5304. Then 15.08 g. (41.5%) of IV, b.p. 185–188° (0.3 mm.), was collected and subjected to redistillation, b.p. 191–191.5° (0.9 mm.), n^{25}D 1.4891, [α]^{25}D 33.9°, [M]^{25}D 123° (*c* 11.1, 95% ethanol).

Anal. Calcd. for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.43; H, 9.21; N, 3.93.

The low-boiling fraction was redistilled. The infrared spectrum (10% in carbon tetrachloride) of the redistilled material exhibited a strong band at 1687 cm.$^{-1}$ and a weaker band at 1732 cm.$^{-1}$, indicating that it probably consisted largely of a five-membered lactam, likely to be 1-(α-methylphenethyl)-2-pyrrolidone, together with a smaller amount of ester. It was dissolved in ether and extracted with 5% hydrochloric acid to remove any basic compounds. The ethereal solution was washed with water, dilute sodium bicarbonate solution and again water, was dried with sodium sulfate, and the ether was removed on the steam-bath. The residue was redistilled through the Holzman column. The center cut boiled at 113.5° (0.15 mm.), $n^{31.5}$D 1.5322, $\nu_{max}^{CCl_4\ (2\%)}$ 1688 cm.$^{-1}$ (no ester band), [α]^{26}D 14.9°, [M]^{26}D 30° (*c* 10.6, 95% ethanol). The analysis was close to that calculated for (+)-1-(α-methylphenethyl)-2-pyrrolidone.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.11; H, 8.51; N, 6.82.

Diethyl (+)-ζ,ζ'-(α-Methylphenethylimino)-bis-enanthate.—A mixture of 13.52 g. (0.10 mole) of (+)-α-methylphenethylamine, 47.5 g. (0.20 mole) of ethyl ζ-bromoenanthate[30] and 27.6 g. (0.20 mole) of potassium carbonate in 100 ml. of absolute ethanol was stirred at reflux for 24 hours. The reaction mixture was worked up as described for IV. After several distillations through a Holzman column, 13.29 g. (30%) of colorless diester was obtained, b.p. 215–216° (0.15 mm.), n^{25}D 1.4838, [α]^{26}D 23.8°, [M]^{26}D 107° (*c* 10.8, 95% ethanol).

Anal. Calcd. for $C_{27}H_{45}NO_4$: C, 72.44; H, 10.13; N, 3.13. Found: C, 72.14; H, 10.08; N, 3.24.

(+)-1-(α-Methylphenethyl)-1-azacycloöctan-5-one (V).—The Dieckman ring closure was carried out using a Morton high speed stirrer assembly[31] and high dilution conditions.[16] To 1.5 l. of dry xylene stirred under nitrogen was added 2.2 g. (0.092 mole) of sodium hydride followed by 0.1 ml. of methanol. The stirring rate was increased, and the xylene brought to vigorous reflux. A solution of 12.72 g. (0.035 mole) of diethyl (+)-γ,γ'-(α-methylphenethylimino)-bis-butyrate (IV) in 300 ml. of dry xylene was added at such a rate that addition was complete in about 24 hours. Occasionally xylene was drawn off from the condenser in such amounts that the volume of the reaction mixture remained approximately constant. The reaction mixture was refluxed for an additional hour after completion of ester addition. Stirring was slowed, and the mixture was allowed to cool. It was then cooled further in an ice-bath, and a solution of 6.6 g. (0.11 mole) of glacial acetic acid in 50 ml. of xylene was added gradually. An additional 50 ml. of xylene was put in to wash the acetic acid–xylene mixture into the flask, and finally 35 ml. of water was added. Nitrogen passage was discontinued. Stirring was continued for a few minutes and then the aqueous layer was separated and discarded. The xylene layer was extracted with three 50-ml. portions of 6 *N* hydrochloric acid. The acid extract was refluxed 6 hours to hydrolyze and decarboxylate the intermediate. The solution was allowed to cool, basified cautiously with solid potassium carbonate, and extracted with five 60-ml. portions of ether. The ethereal solution was dried, the ether was removed on the steam-bath, and the residue was distilled through a Holzman column to yield 4.75 g. (55%) of the aminoketone V as a colorless, viscous, unstable liquid, b.p. 149.5–150.0° (0.5 mm.), n^{32}D 1.5378, $\nu_{max}^{CCl_4\ (10\%)}$ 1686 cm.$^{-1}$; R.D. in methanol (*c* 0.127), 25°, negative Cotton effect superimposed on a positive plain curve: $[\alpha]_{700}$ +9°, $[\alpha]_{589}$ +19°, $[\alpha]_{400}$ +55°, $[\alpha]_{347.5}$ +68°, $[\alpha]_{315}$ +6°, $[\alpha]_{310}$ −54°; (*c* 0.0254) $[\alpha]_{300}$ −157°, $[\alpha]_{295}$ −496°.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.18; H, 9.60; N, 5.83.

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[24] N. J. Leonard, M. Ōki, J. Brader and H. Boaz, THIS JOURNAL, **77**, 6237 (1955).

[25] N. J. Leonard, R. C. Fox, M. Ōki and S. Chiavarelli, *ibid.*, **76**, 630 (1954).

[26] All melting points are corrected. We wish to thank Mrs. Maria Stingl, Miss Claire Higham and Mr. Josef Nemeth for the microanalyses. We also thank Mr. James Brader and Mr. Brian Clooney for the determination of the infrared absorption spectra (other than those run in D_2O using a calcium fluoride cell).

[27] C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4354 (1955).

[28] C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6362, 6377 (1956).

[29] C. Djerassi, J. Osiecki and W. Herz, *J. Org. Chem.*, **22**, 1361 (1957).

[30] N. J. Leonard, R. C. Fox and M. Ōki, THIS JOURNAL, **76**, 5708 (1954).

[31] A. A. Morton, B. Darling and J. Davidson, *Ind. Eng. Chem., Anal. Ed.*, **14**, 734 (1942).

Adding acetic acid to 2 ml. of a solution of V in methanol (*c* 0.0314) in increasing proportion: 1 drop of 10%, 20%, 100% acetic acid, gave a series of $[\alpha]_{300}$ values, respectively: −121°, −16°, +45° (readings identical when taken immediately and after 15 minutes); R.D. for V in 2 *N* HCl (*c* 0.095), 25°, positive plain curve: $[\alpha]_{700}$ +4°, $[\alpha]_{589}$ +6°, $[\alpha]_{400}$ +55°, $[\alpha]_{350}$ +91°, $[\alpha]_{295}$ +148°, $[\alpha]_{275}$ +200°. A 40% (*ca.*) solution of the hydrochloride of V in D_2O in a calcium fluoride cell showed practically no infrared carbonyl absorption (only a slight dip below the base line near 1700 cm.$^{-1}$). The phenyl absorption at 1608 and 1495 cm.$^{-1}$ served as an internal standard for comparison and the carbonyl maximum at 1706 ± 3 cm.$^{-1}$ for 1-*t*-butyl-1-azacyclononan-5-ol-6-one perchlorate served as an external standard.

The perchlorate XI ($X = ClO_4$) of V was formed in ether and recrystallized from methanol–ethyl acetate as colorless plates, m.p. 158.5–160°; $\nu_{\max}^{\text{Nujol}}$ 3320(s), 1606(w), 1587(w), transparent in the 6 μ region.

Anal. Calcd. for $C_{16}H_{24}ClNO_5$: C, 55.57; H, 6.99; N, 4.05; Cl, 10.25. Found: C, 55.52; H, 7.20; N, 4.02; Cl, 10.34.

(+)-1-(α-**Methylphenethyl)-1-azacycloöctan-5-ol (X)**.—To a stirred mixture of 0.95 g. (0.025 mole) of lithium aluminum hydride and 50 ml. of dry tetrahydrofuran was added dropwise a solution of 3.19 g. (0.013 mole) of (+)-1-(α-methylphenethyl)-1-azacycloöctan-5-one (V) in 50 ml. of dry tetrahydrofuran. The mixture was refluxed for 6 hours and then cooled in an ice-bath. The excess lithium aluminum hydride was destroyed by dropwise addition of a solution of 3 ml. of water in 25 ml. of tetrahydrofuran. The mixture was filtered through sintered glass, and the inorganic matter was washed with ten 15-ml. portions of tetrahydrofuran. The tetrahydrofuran solution was dried and the solvent was removed at reduced pressure. Distillation of the residue yielded 2.82 g. (88%) of colorless, viscous oil, b.p. 135–137° (0.15 mm.), $n^{25}\mathrm{D}$ 1.5356, $\nu_{\max}^{CCl_4\,(10\%)}$ 3050 cm.$^{-1}$ (s, broad); R.D. in methanol (*c* 0.100), 26°, positive plain curve: $[\alpha]_{700}$ +2°, $[\alpha]_{589}$ +8°, $[\alpha]_{400}$ +30°, $[\alpha]_{350}$ +60°; (*c* 0.112) $[\alpha]_{320}$ +96°; $[\alpha]_{300}$ +122°; $[\alpha]_{285}$ +156°; R.D. for X in 2 *N* HCl (*c* 0.095), 25°, positive plain curve: $[\alpha]_{700}$ +28°, $[\alpha]_{589}$ + 37°, $[\alpha]_{400}$ +83°, $[\alpha]_{350}$ +121°, $[\alpha]_{320}$ +159°, $[\alpha]_{300}$ +201°, $[\alpha]_{270}$ +267°.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.18; H, 10.30; N, 5.57.

(−)-**N**-(α-**Methylphenethyl)-acetamide (VI)**.—The procedure followed was similar to that described by Welsh,[17] using a cold suspension of 42.0 g. (0.50 mole) of sodium bicarbonate, 300 ml. of water and 27.04 g. (0.20 mole) of (+)-α-methylphenethylamine (III), to which 30.6 g. (0.30 mole) of acetic anhydride was added with shaking. Purification of the product was accomplished by sublimation, yield 30.8 g. (87%), m.p. 121–124° (reported[17] 124°); $\nu_{\max}^{\text{Nujol}}$ 3215, 1644 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ −7.1° (*c* 6.34 in 95% ethanol), $[\alpha]^{25}\mathrm{D}$ −43.5° (*c* 2.00 in chloroform) (reported[17] −44°); R.D. in methanol (*c* 0.115), 25°, negative plain curve: $[\alpha]_{700}$ −12°, $[\alpha]_{400}$ −28°, $[\alpha]_{350}$ −77°, $[\alpha]_{300}$ −163°, $[\alpha]_{270}$ −269°; R.D. for VI in 2 *N* HCl (*c* 0.122), 24°, positive plain curve: $[\alpha]_{700}$ +1°, $[\alpha]_{400}$ +12°, $[\alpha]_{350}$ +16°, $[\alpha]_{300}$ +29°, $[\alpha]_{270}$ +71°.

(+)-**N-Ethyl**-α-**methylphenethylamine (VII)**.—To a stirred mixture of 75 ml. of dry tetrahydrofuran and 4.55 g. (0.12 mole) of lithium aluminum hydride was added a solution of 14.18 g. (0.080 mole) of (−)-N-(α-methylphenethyl)-acetamide (VI) in 50 ml. of tetrahydrofuran at such a rate that the reaction remained under control (over a period of about 15 minutes). When all the amide had been added, the reaction mixture was heated under reflux for 15 hours. The base was isolated in the usual manner and was purified by vacuum distillation, yield 11.0 g. (84%), b.p. 104.5–106° (14 mm.) (reported by Keil and Dobke[32] for the *dl*-compound, 103° (25 mm.)), $n^{25}\mathrm{D}$ 1.4986, $[\alpha]^{29}\mathrm{D}$ 36° (*c* 10.02, 95% ethanol).

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.54; H, 10.40; N, 8.77.

(+)-γ-(**N-Ethyl**-α′-**methylphenethylamino)-butyronitrile (VIII)**.—A mixture of 14.80 g. (0.10 mole) of γ-bromobutyronitrile, 16.33 g. (0.10 mole) of (+)-N-ethyl-α-methylphenethylamine, 13.82 g. (0.10 mole) of anhydrous potassium carbonate and 100 ml. of absolute ethanol was stirred at reflux temperature for 48 hours. The mixture was then cooled, filtered and the salts were washed with three 20-ml. portions of ethanol. The ethanol was removed at reduced pressure and the residue was dissolved in 200 ml. of ether. The ethereal solution was washed with 25 ml. of water, dried, the ether was removed on the steam-bath, and the residue was distilled through a Holzman column to yield 12.49 g. (54%) of colorless product, b.p. 118–119° (0.10 mm.), $n^{25}\mathrm{D}$ 1.5044, $[\alpha]^{26}\mathrm{D}$ 52.9° (*c* 11.11, 95% ethanol).

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.28; H, 9.80; N, 12.25.

(+)-**5-(N-Ethyl**-α-**methylphenethylamino)-2-pentanone (IX)**.—To the Grignard reagent prepared from 3.65 g. (0.15 g.-atom) of magnesium and 17.7 g. (0.125 mole) of methyl iodide in 120 ml. of anhydrous ether was added dropwise a solution of 11.52 g. (0.050 mole) of (+)-γ-(N-ethyl-α′-methylphenethylamino)-butyronitrile (VIII) in 150 ml. of ether. The mixture was then refluxed for 9 hours. It was cooled in an ice-bath, and 250 ml. of 10% hydrochloric acid was added slowly. The mixture was allowed to stand overnight at room temperature and the ether layer as well as considerable amounts of an acid- and ether-insoluble gummy material were separated and discarded. The aqueous layer was basified with 150 ml. of 25% aqueous sodium hydroxide solution and then extracted with four 200-ml. portions of ether. The ether extracts were dried, the ether was removed on the steam-bath, and the residue was distilled through the Holzman column as a colorless, viscous oil, yield 4.29 g. (35%), b.p. 123.5–124° (0.30 mm.), $n^{25}\mathrm{D}$ 1.5023, $\nu_{\max}^{CCl_4\,(2\%)}$ 1720 cm.$^{-1}$ (s); R.D. in methanol (*c* 0.212), 25°, positive plain curve: $[\alpha]_{700}$ +13°, $[\alpha]_{589}$ +26°, $[\alpha]_{400}$ +68°; (*c* 0.056) $[\alpha]_{350}$ +105°, $[\alpha]_{300}$ +143°, $[\alpha]_{275}$ +175°; R.D. for IX in 2 *N* HCl (*c* 0.159), 26°, positive plain curve: $[\alpha]_{700}$ +8°, $[\alpha]_{589}$ +13°, $[\alpha]_{400}$ +38°, $[\alpha]_{350}$ +56°, $[\alpha]_{295}$ +86°.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.45; H, 9.90; N, 5.37.

The picrate and perchlorate were formed in ether, but both proved to be oils. The perchlorate was washed four times with dry ether and dried at 56° *in vacuo*. Some decomposition occurred on drying as the compound developed color, becoming an extremely viscous yellow oil. The infrared spectrum (liquid film) exhibited a medium broad band at about 3380 cm.$^{-1}$ (probably due to water) and strong bands at 3090 cm.$^{-1}$ and 1703 cm.$^{-1}$. The spectrum is consistent with its formulation as the N-protonated salt.

Methiodide of 1-Methyl-1-azacyclononan-5-ol-6-one (XIIa).—A solution of 0.51 g. (3.0 mmoles) of XIIa[25] in 1.0 ml. of methyl iodide was refluxed for 1 hour on the water-bath, and most of the excess methyl iodide was removed by distillation. The residue was dissolved in 1.5 ml. of boiling glacial acetic acid. The hot solution was cooled, and the colorless methiodide was removed by filtration and dried *in vacuo*. The methiodide was very hygroscopic and quite unstable. The yield was 0.50 g. (53%) of material melting at 126–155° dec. which gave an immediate yellow precipitate with aqueous silver nitrate. The infrared spectrum (Nujol mull) exhibited strong maxima at 3350 and 1703 cm.$^{-1}$.

Benzobromide of 1-Methyl-1-azacyclononan-5-ol-6-one (XIIa).—A mixture of 0.51 g. (3.0 mmoles) of XIIa and 1.07 ml. (1.54 g. or 9.0 mmoles) of benzyl bromide was heated for 1 hour in a water-bath maintained at 75–85°. A very viscous phase separated during the reaction. The viscous material was washed by decantation with 5 ml. of pentane, dissolved in a small amount of ethanol and ethyl acetate added until a cloudiness was produced. The cloudiness was cleared by addition of a few drops of ethanol. The solution was filtered, cooled in an ice-bath and scratched to induce crystallization. Recrystallization from ethanol-methanol gave colorless prisms, m.p. 200.5–205° dec.; $\nu_{\max}^{\text{Nujol}}$ 3240, 1707 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{24}BrNO_2$: C, 56.15; H, 7.07; N, 4.09. Found: C, 56.02; H, 7.33; N, 4.06.

1-Methyl-1-azacyclononan-5-ol-6-one Picrate.—Formed from XIIa and picric acid in methanol, the picrate was

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[32] F. Keil and W. Dobke, German Patent 767,263, March 31, 1952; *C. A.*, **47**, 2772 (1953).

twice recrystallized from the same solvent, yellow needles which blackened in the range 247–257° and finally melted at 261°; ν_{max}^{Nujol} 3500, 3140 cm.$^{-1}$, transparent in the range 1750–1650 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{20}N_4O_9$: C, 45.00; H, 5.04; N, 14.00. Found: C, 45.02; H, 4.99; N, 13.99.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

Ouabagenin. III. Assignment of the Sixth Hydroxyl Group and a Structural Correlation with Strophanthidin

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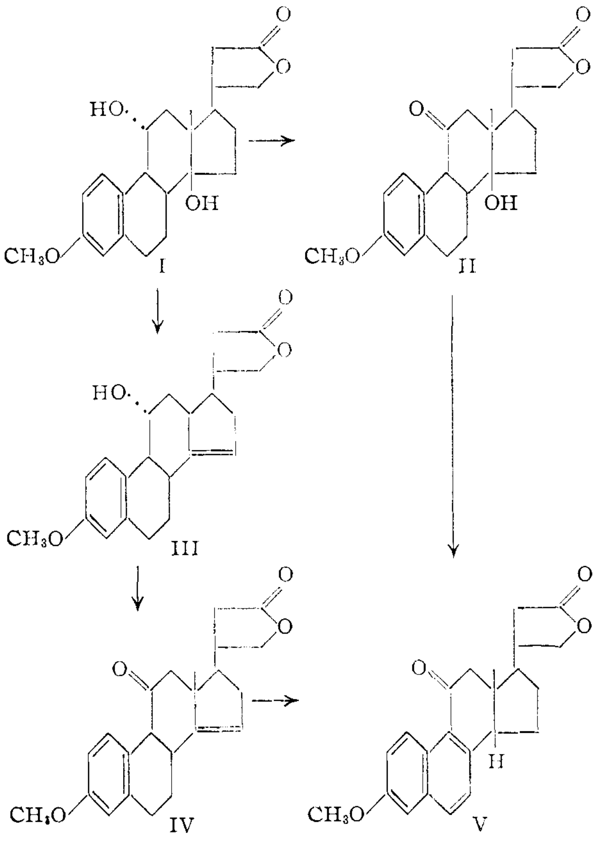
Degradation of ouabagenin to a product (V) possessing a keto group conjugated with a naphthalene system (rings A and B) establishes the fact that ouabagenin contains a secondary hydroxyl group at C.11. Conversion of strophanthidin and of ouabagenin into a common derivative (Xb), still possessing the C.14 hydroxyl group and lactone side chain, provides additional evidence for the β-orientation of these functions in the latter genin and establishes a direct structural correlation between ouabagenin and other aglycones of the *Strophanthus* group.

In previous papers[2] evidence has been presented which permits assignment of four of the six hydroxyl groups of ouabagenin to the 1-, 3-, 5- and 19-positions, respectively. The further inference that a tertiary hydroxyl group is located at C.14 has been drawn from the early observation of Jacobs and Bigelow[3] that the parent rhamnoside, ouabain, is converted into isoöuabain by the action of base, and from the results of various dehydration experiments, notably those of Meyrat and Reichstein.[4] The position of the remaining (secondary) hydroxyl function has remained uncertain, although a tentative assignment of this group to C.11 was made by Fieser and Newman[5] as early as 1936. The Fieser–Newman suggestion, while based on arguments that are no longer tenable,[6] was incorporated in the 1942 formulation of Mannich and Siewert,[7] and has received some support from work of Tschesche and Snatzke[8] in which epimerization of the hydroxyl group in question (by oxidation to the ketone and sodium borohydride reduction) furnished a derivative possessing a non-acylable secondary hydroxyl function. This behavior is characteristic of 11β-hydroxy steroids. Since all of the secondary hydroxyl groups of ouabagenin are readily acetylated, Tschesche and Snatzke were led to the conclusion that ouabagenin is an 11α-hydroxy compound. On the other hand, Djerassi and Ehrlich[9] have argued for an alternative assignment (presumably C.6) on the basis of the unsupported assumption that the very slow reaction of ouabagenin with lead tetraacetate represents the cleavage of a 1,2-glycol.

We have recently reported definitive evidence in support of the 11-hydroxy structure.[10] The present paper describes the details of this work as well as experiments that establish a direct structural correlation between ouabagenin and other aglycones of the *Strophanthus* group.

When the diol I[2a] is oxidized with the chromium trioxide–pyridine complex, a ketol II is obtained which shows only anisole absorption in the ultraviolet. The absence of a conjugated carbonyl system in this substance is further indicated by the position (5.80 μ) of the ketonic absorption band in the infrared. Compound II proved resistant to dehydration by hydrogen chloride in chloroform at 0°, and under more vigorous conditions (hydrogen chloride in refluxing methanol and p-toluenesulfonic acid in refluxing benzene) oily products were obtained that could not be induced to crystallize.



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[1] Public Health Service Predoctoral Fellow, 1956–1958.

[2] (a) R. P. A. Sneeden and R. B. Turner, *Chemistry & Industry*, 1235 (1954); THIS JOURNAL, **77**, 130 (1955); (b) K. Florey and M. Ehrenstein, *J. Org. Chem.*, **19**, 1174 (1954); (c) Ch. Tamm, *Helv. Chim. Acta*, **38**, 147 (1955); (d) E. J. Becker and M. Ehrenstein, *Ann.*, **608**, 54 (1957).

[3] W. A. Jacobs and N. M. Bigelow, *J. Biol. Chem.*, **96**, 647 (1932); **101**, 15 (1933).

[4] A. Meyrat and T. Reichstein, *Helv. Chim. Acta*, **31**, 2104 (1948).

[5] L. F. Fieser and M. S. Newman, *J. Biol. Chem.*, **114**, 705 (1936).

[6] See the discussion of this point in ref. 2a.

[7] C. Mannich and G. Siewert, *Ber.*, **75**, 737, 750 (1942).

[8] R. Tschesche and G. Snatzke, *ibid.*, **88**, 1558 (1955).

[9] C. Djerassi and R. Ehrlich, *J. Org. Chem.*, **19**, 1351 (1954).

[10] R. B. Turner and J. A. Meschino, THIS JOURNAL, **78**, 5130 (1956)